I. REMARKS:

A. Status of the Claims

Claims 1-3 were originally filed with the case on December 5, 2003. Claims 1-3 were rejected in an Official Action, mailed on November 17, 2004. Claims 1 and 3 were amended and claims 4-7 were added in a Response to Office Action filed on May 17, 2005. All claims were rejected in an Official Action mailed on July 29, 2005. No claims were amended, added, or canceled in the Response to Office Action filed on November 29, 2005. Claims 1-7 are rejected in the present Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. The Claims are not Obvious under 35 U.S.C. § 103(a).

In the first Office Action issued in the case, all claims were rejected as being obvious over U.S. Patent No. 5,075,116 (LaHaye); U.S. Patent No. 6,046,188 (Malfroy-Camine). In the second Office Action, LaHaye and Malfroy-Camine were again cited and Campbell and Crapo were added to the obviousness rejection. The present Action again cites LaHaye, Malfroy-Camine, Campbell and Crapo and now adds Winkler to the growing list of references that are asserted to obviate the claimed invention when considered together.

Malfroy-Camine is said to teach the use of the claimed compounds as antioxidants for the treatment of diseases by acting as a free radical scavenger. The first Action acknowledges that Malfroy-Camine lacks a teaching the treatment of macular degeneration, diabetic retinopathy or retinal edema. LaHaye is said to teach the use of free radical scavengers and antioxidants for treating diseases such as macular degeneration. Campbell is said to teach the use of the claimed compounds in a

pharmaceutical formulation which can be administered by any appropriate route of administration, such as injection. The second Action acknowledges that Campbell lacks a teaching of the use of the compounds described to treat ocular disorders such as macular degeneration. Crapo is said to teach that compounds with a porphyrin ring, which are said to be SOD mimetics, can be used to treat disorders such as glaucoma and macular degeneration. Winkler is said to teach the role of oxidation in relation to macular degeneration and the effect of superoxide dismutase in preventing oxidative damage. The present Action asserts that these five references, taken together, teach the general concept that compounds having superoxide dismutase activity can be used for the prevention of oxidative damage and conditions such as macular degeneration. Applicants respectfully traverse.

The Examiner states that LaHaye and Malfroy-Camine motivate the innovative use of compound A[1] to treat AMD, delivered by ocular injection. However, the Federal Circuit states that prior art must suggest or motivate the combination of references for an obviousness rejection to be valid. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1368 (Fed. Cir. 1996). This requirement avoids obviousness in hindsight where the specification "guide[s]" the Examiner "through a maze of prior art references". *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988). We respectfully suggest that the Application is a concrete advancement in the art and is not motivated by prior work. The following argument seeks to refute the obviousness rejection set forth in the present Action. *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984).

The rejection relies on a number of references, fragments of which have been pasted together to form the portrait of the presently claimed invention. For example,

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Malfroy-Camine appears to describe only the use of antioxidant salen-transition metal complexes for the treatment of cataracts (not retinal diseases), LaHaye simply associates general vitamin antioxidants and the treatment of macular degeneration, Campbell is said to give an example of one type of delivery method, and Crapo is said to describe poryphrin ring molecules, which are vastly different from the presently claimed compounds, that can be used against AMD. The new reference, Winkler, is said to show the use of superoxide dismutase (and not its mimetics) against macular degeneration. Winkler lacks a description of any of the compounds for use in the methods of the claimed invention.

It is submitted that this is precisely the "maze of prior art references" against which *Grain Processing* warns. 840 F.2d at 907. In order for the leap from the teachings in the prior art to the claimed invention to be "obvious", an inventor would have to piece together fractions of each reference to arrive at the present set of claims.

As acknowledged in the first Office Action, Malfroy-Camine does not teach the use of compound A to treat retinal maladies, such as AMD. Nor does it suggest any possibility of delivery methods that can reach the rear part of the eye. In fact, the expression of a narrow reference to cataracts without a broader claim to eye treatment counsels a narrow construction of Malfroy-Camine. *See Phillips v. AWH*, 376 F.3d 1382 (Fed. Cir. 2004), *also expressio unius est exclusio alterius* (canon of construction, expression of the one is the exclusion of the other.)

Cataracts are a disorder affecting the lens of the eye, whereas retinal disorders, such as AMD, affect the retina. It is well known by the skilled artisan that the retina and the lens have very different properties. The lens is an avascular tissue of terminally differentiated cells that are not shed throughout the lifetime of an individual, has

relatively low metabolic turnover, and has nutrition supplied by the aqueous humor. *See*, *e.g.*, Bron, 214 Ophthalmologica 86 (2000). The lens lies posterior to the aqueous humor and anterior to the vitreous, and is significantly anterior to the retina.

The retina, in contrast, is a highly vascularized tissue containing many different cell types--such as photoreceptors, retinal pigmented epithelial (RPE) cells, microglia, and retinal ganglion cells (RGCs)--that functions to convert incoming light signals to electrical information, which it transmits to the brain. Photoreceptors absorb incoming light through their opsin-bound retinaldehyde chromophores, and transduce this event into an electrical signal. This signal is relayed through intermediary cells to RGCs and thence to the relevant portion of the brain for interpretation. Unlike lens cells, several different types of retinal cells have high metabolic demand. For example, photoreceptors constantly shed and replace their outer segments, which are phagocytozed by RPE cells. RPE cells also recycle bleached *trans*-retinaldehdye into the photoactive *cis* form for re-supply to photoreceptors. They also recycle/transport polyunsaturated fatty acids from digested membrane outer segments back to photoreceptors. E cells are considered to be among the most active phagocytozing cells in the body. Bazan, N.G. 29 Trends in Neuroscience 263 (2006); J. Toyoda, *Retinal Basis of Vision* (1999). In sum, it would not be obvious to the skilled artisan to consider a compound that treats the lens of the eye, an avascular tissue, for the treatment of disorders of the retina, a vascular tissue that functions quite differently from the lens.

Winkler appears to discuss the relationship between oxidative damage and AMD. The focus of the paper is on the physiological effects of oxidative damage on the retinal tissues. Figure 1 is said to show an "armory of protectants," including antioxidant enzymes, one of which is superoxide dismutase. Winkler does not provide a detailed

discussion of the treatment of AMD, much less of the general use of SOD mimetics to treat AMD.

The structural differences between the compounds used in the methods of the present invention and the Crapo and Campbell molecules also cannot motivate the present innovation. *See* (Resp. to Office Action ¶¶ 4-5, Nov. 29, 2005). The lower molecular weight of compound A has a direct effect on the potential bioavailability improvements, and is an essential component of the uniqueness of the present invention. *Id.* One of the objects of the present invention is to provide lower molecular weight compounds that catalyze superoxide disproportionation with efficiency comparable to endogenous Mn SOD, while avoiding the bioavailability and immunogenic issues thought to be due to the higher molecular weight species (Spec. page 7, lines 18-24). In fact, the primary structural similarity arises from the manganese ion common to each group of structures. As an infinite number of compounds could use manganese ions as their functional site, this basic similarity is not sufficient to support an inference of motivation.

Campbell is said to infer a motivation to apply one antioxidant structure using a type of ocular injection. However, the structure is so different that it does not give an adequate motivation to combine when read with the cataract assertion in Malfroy-Camine. In addition, LaHaye, which has a compound closer in structure to compound A, only envisions application in tablet form. The idea of using these particular lower molecular weight compounds, with this type of injection method, for this important disease of age-related macular degeneration is first described by the present inventors.

It is submitted that the Action has taken the teaching of the present application and combined it with the disclosure in Campbell or Crapo that certain different and larger compounds are SOD mimetics or oxidant scavengers and may be useful to treat a variety

of disorders other than AMD, DR or retinal edema, to state that it would have been obvious for one skilled in the art to treat these disorders with the smaller compounds of the present invention. This amounts to an improper "hindsight reconstruction" of the invention based upon the teaching in the present application. *See In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). In *Fine*, the court explained that

> [t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Fine, 5 U.S.P.Q.2d at 1600 (quoting *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983)).

The rejection under § 103 based on the combination of Malfroy-Camine, LaHaye, Campbell and Crapo, and now Winkler, amounts to a "picking and choosing" of certain parts of a growing number of references while ignoring other aspects of it. The Federal Circuit has held that "it is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference *fairly suggests* to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (CCPA 1965)). What the Action ignores is the fact that nowhere within any of the cited references is a method for treating AMD, DR, and/or retinal edema via administration of the described compounds taught or suggested.

In light of the foregoing arguments, Applicants respectfully request that the

obviousness rejection be withdrawn.

C. Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: September 8, 2006